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ATTORNEY DOCKET NO. 00786/428002

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Denise Faustman	Confirmation No.:	2917
Serial No.:	10/713,679	Art Unit:	1644
Filed:	November 14, 2003	Examiner:	Amy E. Juedes
Customer No.:	21559		
Title:	SCREENING METHODS TO IDENTIFY TREATMENTS FOR AUTOIMMUNE DISEASE		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DENISE FAUSTMAN, M.D., Ph.D.

I declare:

1. I am the named inventor of the subject matter described and claimed in United States Patent Application Serial No. 10/713,679 (the "'679 application"), which was filed on November 14, 2003.

2. I am an Associate Professor of Medicine at Harvard Medical School and Director of the Immunobiological Laboratories at the Massachusetts General Hospital. I am also a member of the American Association for the Advancement of Science and co-editor in chief of the Journal of Women's Health. In addition, I am a senior author of over 100 peer-reviewed publications in internationally recognized scientific journals.

3. I have read and understood the Office Action mailed on March 13, 2007. This Declaration is presented to overcome the rejection of claims 12-15, 18, and 20-21 under 35 U.S.C. § 112, first paragraph, for lack of enablement. I have considered the Office's remarks regarding the teachings of the specification with respect to the scope of the present claims.

4. A discovery that formed a basis for the '679 application was that autoreactive immune cells (e.g., leukocytes) responsible for development of autoimmune diseases are sensitive to (i.e., are killed by) exposure to TNF-α and TNF-α inducers (e.g., agonists), which induce death in these cells. These cells contain genetic defects that alter NF-κB activity; these defects are a common denominator across several autoimmune diseases, including the following: Type I diabetes, lupus, Crohn's disease, Sjogren's syndrome, autoimmune glandular diseases [autoimmune polyendocrinopathy syndrome (APS)-1 or autoimmune polyendorinopathy candidasis ectodermal dystrophy], hypothyroidism, multiple sclerosis, psoriasis, and scleroderma. My data demonstrate that multiple, disparate autoimmune diseases can be diagnosed in a mammal, according to the methods of present claims 12-15, 18, and 20-21, based on the sensitivity of autoreactive immune cells responsible for, or responsible for exacerbating, autoimmune disease to TNF-α agonists, such as TNF-α or other TNF-α inducing substances, which promote autoreactive immune cell death.

5. I conducted additional experiments that support and further validate the data reported in the specification. The data reported in the specification, and in this declaration, provide clear evidence that autoreactive immune cells are sensitive to TNF-α, and thus, that administration of TNF-α, and agonists of TNF-α, to these cells promotes their death. In particular, the specification discloses that exposure of autoreactive leukocytes from NOD mice, which is an accepted animal model of type 1 (autoimmune) diabetes mellitus, Sjogren's

syndrome, and lupus in humans, to TNF-α, which is normally cytoprotective in normal leukocytes, causes death to autoreactive leukocytes. These data are presented in the specification at, e.g., page 18, lines 4-18; and page 57, line 6, through page 60, line 9, which teaches that autoimmune leukocytes from NOD mice and humans die after exposure to TNF-α and TNF-α inducing substances, such as BCG. In contrast, control leukocytes from normal NOD mice and humans do not exhibit decreased viability.

6. Researchers working under my direction conducted additional experiments that support and further validate the data reported in the specification. The results of these experiments, which involve the use of autoreactive immune cells obtained from patients having several disparate autoimmune diseases, show that the methods of the invention are efficacious (see Exhibit A). In particular, we observed that autoreactive leukocytes cells obtained from human patients diagnosed with Type I diabetes, lupus, scleroderma, Sjogren's syndrome, hypothyroidism, multiple sclerosis, Crohn's disease, and psoriasis are also sensitive to TNF-α agonists, such as TNF-α. Similarly to the autoreactive leukocytes cells from NOD mice, autoreactive leukocytes from patients having these autoimmune diseases, when exposed to TNF-α, experience cell death. Thus, these data confirm that defects in the NF-κB signaling pathways in autoreactive immune cells play a role in disparate autoimmune diseases and can be used to diagnose a mammal with autoimmune diseases or determine a mammal's predisposition to develop autoimmune disease.

In culture, we observed that autoreactive leukocytes from patients diagnosed with various different autoimmune diseases die when exposed to a TNF-α agonist. We observed this result in over 1000 type 1 diabetics studied, and in our studies of 50 patients with lupus, 8 patients with scleroderma, 8 patients with Sjogren's syndrome, 50 patients with hypothyroidism, 20 patients with multiple sclerosis, 15 patients with Crohn's disease, and 6 patients with psoriasis. Our results show that autoreactive immune cells can be distinguished from normal cells not only by defects in NF-kB on a molecular level, but also on a cellular level by targeted cell death with TNF-α agonism, which is a symptom of the NF-kB interruption.

7. We also confirmed that TNF-α agonists other than TNF-α promote autoreactive immune cell death. We demonstrated that TNF agonist antibodies promote cell death in autoreactive immune cells from patients having diabetes, lupus, multiple sclerosis, psoriasis, Crohn's, and rheumatoid arthritis (see Exhibit B). Exhibit B, which presents an average of data from experiments performed using cells obtained from patients having each of the indicated autoimmune diseases, clearly shows that even low dose exposure to TNF-α agonist antibodies results in autoreactive immune cell death.

8. In addition to TNF-α and TNF-α agonist antibodies, we further confirmed that other substances that induce endogenous TNF-α expression promote autoreactive immune cell death. For example, BCG, a well known inducer of endogenous TNF-α, promotes the death of autoreactive immune cells from NOD mice. These data demonstrate selective autoreactive immune cell elimination by a TNF-α inducer substance in the same manner as that observed using TNF-α and TNF-α agonist antibodies.

9. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were
made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. ∋ 1001 and that such willful false statements may jeopardize the validity of the application and any patents issued thereon.

9/12/07
Date

Denise Faustman, M.D., Ph.D.

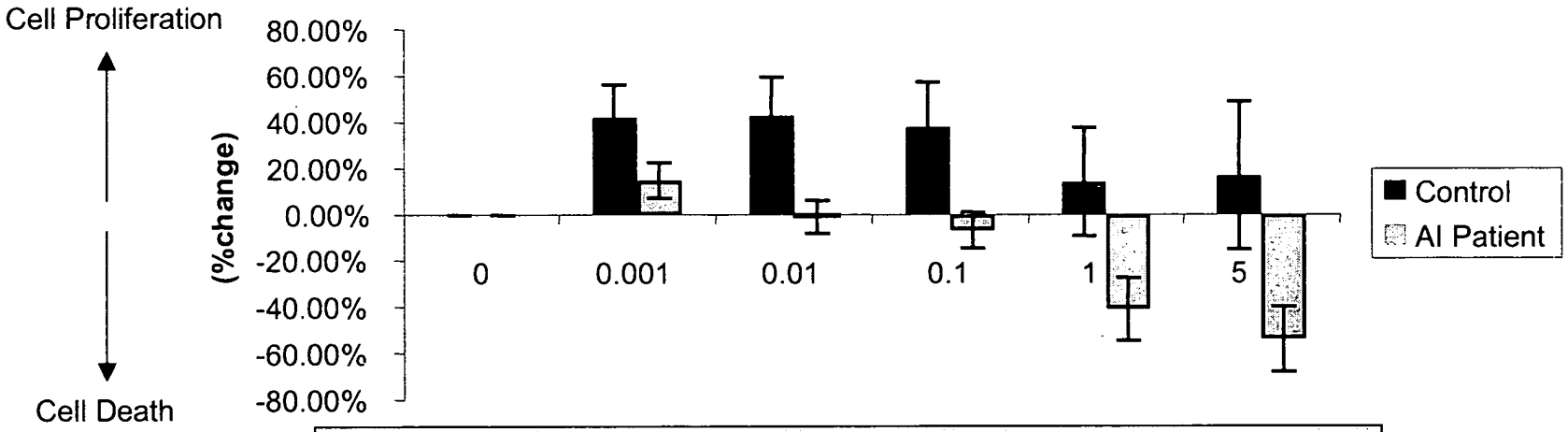
Exhibit A

Humans with diverse autoimmune diseases have T cells with TNF induced death

	Autoimmune Samples studied
• Type 1 diabetes	>1000
• Lupus	>50
• Scleroderma	>8
• Sjogren's Syndrome	>8
• Hypothyroidism	>50
• Multiple sclerosis	>20
• Crohn's	>15
• Psoriasis	6

Exhibit B

TNF Agonism Promotes Autoimmune Cell Death



TNF agonist antibody selectively kills autoimmune T cells

	T test
0.001	0.041599
0.01	0.020108
0.1	0.050111
1	0.036054
5	0.025789